

Remarks

Claims 1-9, 12-23, 25, 26 and 32-34 were pending in this application. Claims 2-8, 15-17, 19, 24, 27-32 and 34 are canceled. Applicants expressly reserve the right to pursue protection of any or all of the subject matter of the canceled claims in a subsequent application. Rejections of canceled claims are hereafter treated as moot. Claims 1, 9, 18, 23 and 33 have been amended.

Support for claim amendments can be found throughout the specification and the claims as originally filed. No new matter is introduced by these amendments.

After entry of this amendment **claims 1, 9, 12-14, 18, 20-23, 25, 26 and 33 are pending in this application.**

Interview with Examiner Kim

Applicants thank Examiner Kim for discussing the pending Office action with their undersigned representative on August 19, 2008. During this interview, the mode of administration of a drug combination comprising neostigmine and glycopyrrolate was discussed. In particular, Applicants' representative stated that the cited art does not teach, suggest, or disclose intra-nasal administration of a drug combination including neostigmine and glycopyrrolate or the effective amount/ratio of neostigmine and glycopyrrolate for the treatment of chronic pseudo-obstruction.

Although an agreement was not reached, Examiner Kim agreed to consider Applicants arguments and amendments made herein. It is believed that this response is prepared in accordance with suggestions made by Examiner Kim.

Claim Rejections under 35 U.S.C. §103:

Claims 1-9, 12-23, 25, 26 and 32-34 were rejected under 35 U.S.C. §103 as allegedly being obvious in light of Ponec *et al.* (*New England J. Med.* 341(3): 137-141, 1999; hereinafter Ponec *et al.*) in view of Vavilala *et al.* (*New England J. Med.* 341(21): 137, 1999; hereinafter Vavilala *et al.*). Applicants traverse this rejection.

Ponec *et al.* disclose intravenous administration of neostigmine for the treatment of acute

colonic pseudo-obstruction. Acute colonic pseudo-obstruction is massive dilation of the colon without mechanical obstruction that occurs following surgery or acute illness. Ponec *et al.* teach that a side effect of the administration of neostigmine is bradycardia.

Vavilala *et al.* teach that because bradycardia is a complication of neostigmine therapy, another antimuscarinic agent can be administered, such as glycopyrrolate, to minimize bradycardia. Vavilala *et al.* disclose using glycopyrrolate with continuous monitoring by electrocardiography and blood pressure assessment following neostigmine administration in the operating room.

To establish a *prima facie* case of obviousness, the Examiner must identify all of the claimed elements in one or more prior art references and provide a motivation or suggestion to combine or modify the prior art references coupled with a reasonable expectation of success (MPEP §2143).

The Office has failed to establish a *prima facie* case of obviousness because all of the claim elements are not taught, suggested or disclosed by the cited references. At best, Ponec *et al.* in view of Vavilala *et al.* teach intravenous administration of neostigmine and glycopyrrolate to treat acute colonic pseudo-obstruction with continuous monitoring including simultaneous electrocardiography and blood pressure assessment. Neither Ponec *et al.* or Vavilala *et al.* disclose, suggest or render obvious “a method of bowel care comprising chronically administering intra-nasally a therapeutically effective amount of a drug combination comprising neostigmine and glycopyrrolate to a subject having chronic intestinal pseudo-obstruction to relieve chronic constipation, wherein the chronic intestinal pseudo-obstruction is a result of spinal cord injury and the ratio of neostigmine to glycopyrrolate is 2.5:1 to 10:1 by weight” as presently required by the amended claims. In addition, neither Ponec *et al.* or Vavilala *et al.* disclose the administration of neostigmine and glycopyrrolate by a trans-nasal spray as presently required by claims 18 and 23. Because the references cited by the Examiner fail to teach or suggest all of the elements of the claims, such references cannot serve as the basis of a rejection of the claims under 35 U.S.C. §103(a).

Given the teachings of Ponec *et al.* and Vavilala *et al.* on the treatment of acute colonic obstruction and the continuous monitoring used in the operating room, one of skill in the art would not predict that the disclosed therapy would be of use on a chronic basis in a non-clinical setting. There is

no motivation provided in the cited prior art for intranasal administration or to use the ratio of neostigmine to glycopyrrolate that would be needed to treat chronic pseudo-obstruction. As such, Ponec *et al.*, alone or in combination with Vavilala *et al.*, do not teach, suggest, or disclose a method of bowel care for a subject having chronic constipation associated with chronic intestinal pseudo-obstruction as presently claimed.

The Office has not Made the Factual Findings Required to Make a Rejection Under the “Obvious to Try” Rationale

In addition to failing to disclose all of elements of the pending claims, the proposed modification of the references would not be obvious because one of ordinary skill in the art would not have thought that the claimed methods were “obvious to try” in view of Ponec *et al.* and/or Vavilala *et al.* To make up for the lack of teaching present in the cited references, the Office asserts that “Ponec *et al.* suggests that the concomitant treatment with neostigmine and glycopyrrolate can be used for treating colonic pseudo-obstruction” and that such finding “would have prompted the skilled worker to employ the combination in colonic pseudo-obstruction in general including chronic.” (Office action, pages 3 and 4. The Office also asserts that the “amounts of active agent (glycopyrrolate) to be used, the pharmaceutical forms, *e.g.*, tablets, etc., route of administration (intranasal) and cause of resulted condition are all deemed obvious since they are all within the knowledge of the skilled pharmacologist.” (Office action, page 7). However, the Office has not established a *prima facie* case of obviousness because the factual findings necessary to make an “obvious to try” rejection have not been made.

The Office cites *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 82, 127 S.Ct. 1727 (S.Ct. 2007) and the “obvious to try” rationale in rejecting the claims as obvious in view of Ponec *et al.* The USPTO issued guidelines for making a rejection based on the “obvious to try” rationale in the Federal Register vol. 72, No. 195, page 57532, October 10, 2007. The guidelines list the four elements required for making a rejection based on the “obvious to try” rationale as:

- (1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve the problem;
- (2) a finding that there had been a finite number of identified, predictable potential solutions to the art recognized need or problem;

(3) a finding of that one of ordinary skill in the art could have pursued the known potential solution with a reasonable expectation of success; and

(4) whatever additional findings based on the *Graham* factual inquires may be necessary, in view of the facts under consideration, to explain a conclusion of obviousness."

The guidelines further stipulate that, "if any of these factual findings cannot be made, then this rationale cannot be used to support a conclusion that the claim would have been obvious to one of ordinary skill in the art" (*emphasis added*). The Office has not made the required factual findings and therefore Applicants request that this rejection be withdrawn.

The Office has not established a *prima facie* case of obviousness in view of Ponec *et al.* with respect to the pending claims at least because the required factual findings specified in elements (1), (2) and (3) of the "obvious to try" rationale have not been made.

The first element required to make a rejection based on the "obvious to try" rationale has not been met because the Office has not made a factual finding that there was a recognized problem or need in the art. The Office has merely stated that an ordinary practitioner would have been prompted to employ the combination in chronic colonic pseudo-obstruction. However, the Office has not set forth that at the time of invention there had been a recognized problem or need in the art to treat chronic colonic pseudo-obstruction with pharmaceutical agents. Applicants submit that the claimed methods were designed to overcome a specific problem recognized by Applicants, which was the need to find alternative methods of bowel care which at the time of the invention typically involved thrice weekly use of strong laxatives, large numbers of enemas, and potentially traumatic stimulation of the rectum with an assistive device throughout the lifetime of the affected individual. Applicants recognized the need for alternative bowel care methods that included the use of pharmaceuticals through non-invasive modes of administration. In order to satisfy these objectives, the Applicants designed a method of bowel care that could be administered intra-nasally. In the absence of a factual finding of an art recognized problem, namely the ineffectiveness of any prior physical methods, the Office has not met the requirements for rejecting the claims as "obvious to try."

The second element of the "obvious to try" rationale has not been met because the Office has

not made the factual finding that there are a “finite number of identified, predictable potential solutions to the art recognized need or problem.” As discussed above, prior to Applicants’ disclosure, there was no art that recognized the problem or need in the art to treat chronic colonic pseudo-obstruction with pharmaceutical agents. Without an art recognized problem there can be no “finite number of identified, predictable potential solutions to the art recognized need or problem,” that would be obvious to try. Furthermore, even if there were a finite number of identifiable solutions one of ordinary skill in the art using the teaching of using the teaching of Ponec *et al.* and/or Vavilala *et al.* could not have predicted that the disclosed drug combination could be administered chronically, intra-nasally, or that a particular ratio of neostigmine and glycopyrrolate would be found to be effective. Because the Office has not shown that there are a finite number of identifiable and predictable solutions to an art recognized problem, the Office has not made the second factual finding required for an “obvious to try” rejection.

The third element needed to make a rejection based on the “obvious to try” rationale is not met because there is no reasonable expectation that one of ordinary skill in the art could have pursued the known potential solution with a reasonable expectation of success. Absent the Applicants’ disclosure of a method of bowel care including “chronically administering intra-nasally a therapeutically effective amount of a drug combination comprising neostigmine and glycopyrrolate to a subject having chronic intestinal pseudo-obstruction to relieve chronic constipation” as presently claimed, one of ordinary skill in the art would not reasonably believe that such method could be used on a chronic basis or administered intra-nasally. Again, the cited art specifies that the composition is to be administered intravenously and under closely monitored conditions. From these teachings, one would not have had a reasonable expectation of success of using the drug combination in a chronic setting without the continuous monitoring and *via* an alternative mode of administration (*e.g.*, intranasally). In view of the above arguments, the Office has not made a factual finding for the third required element of an obvious to try rejection.

The Office has not established a *prima facie* case of obviousness with respect to the pending claims because at least the first three factual findings required for an obviousness rejection based on the “obvious to try” rationale have not been made. Applicants assert that all pending claims are

therefore allowable in view of the cited references and request that the §103 rejection of these claims be withdrawn.

CONCLUSION

The cited references do not render the pending claims obvious because the claims do not teach or suggest the claimed methods of bowel care. Elements of the claims are missing from the cited references. The Office has also not established a *prima facie* case of obviousness based on the "obvious to try" rationale because the Office has not demonstrated that the elements required to make such a rejection.

Based on the foregoing amendments and arguments, the claims are in condition for allowance and notification to this effect is requested. If for any reason the Examiner believes that a telephone conference would expedite allowance of these claims, please telephone the undersigned at (503) 595-5300.

Respectfully submitted,

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